Bayer

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Consumer Care Division

Gary S. Balkema
President
Region Head Northern Americas

February 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for Ephedrine, Dihydroetorphine, Remifentanil, and Certain Isomers – Docket 98N-0148, 64 Fed. Reg. 1629

Dear Sir/Madam:

I am the President of Bayer Corporation, Consumer Care Division (Bayer) one of the nation's leading over-the-counter health care businesses. Bayer is known for brands such as Bayer Aspirin®, Aleve®, Alka-Seltzer®, Femstat 3®, Flintstones® and One-A-Day Vitamins® and Bronkaid.

On January 11, 1999, the Food and Drug Administration (FDA) published the above-referenced notice requesting comments concerning recommendations by the World Health Organization (WHO) to impose international restrictions, under international treaties, on certain drug substances, including ephedrine. The notice stated that this information would be considered in preparing the U.S. position for a meeting of the United Nations (UN) Commission on Narcotic Drugs to be held in Vienna in March 1999.

On behalf of Bayer, I am writing to urge the U.S. Government to oppose the WHO recommendation that ephedrine be scheduled under the UN Convention on Psychotropic Substances (UN Convention). The WHO recommendation is unsupported by adequate data and is misplaced. At its best, the WHO recommendation is inconsistent with established U.S. policies. The FDA has already found that ephedrine and certain ephedrine combination drug products are generally recognized as safe and effective when properly labeled for OTC use. We are not aware of abuse data to question any of the approved uses.*

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Ephedrine Is Not An Appropriate Drug For Scheduling.

Ephedrine has a long and well-established safety and efficacy profile for its intended use as a nonprescription bronchodilator. The FDA Final Monograph on Bronchodilator Drug Products notes that its OTC availability provides asthmatics with ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room.[1] "This availability especially benefits those asthmatics whose attacks are triggered by common environmental factors (primarily exertion, anxiety, exposure to cold, etc.) when immediate use may be essential."[2]

Additionally, FDA has found that ephedrine is generally recognized as safe and effective in appropriate cream, lotion and ointment preparations for the temporary reduction of swelling associated with hemorrhoids.[3]

The WHO Concerns Do Not Establish A Sufficient Basis For Scheduling.

The UN Convention is, and should remain focused on risk-benefit analysis of substances themselves. It should not focus on substances as possible precursors.** The WHO assessment criteria under the UN Convention for risks and benefits of substances are as follows: (1) a substance's capacity to produce a state of dependence, and central nervous system stimulation or depression resulting in hallucinations or disturbances in motor function, thinking, behavior, perception or mood, (2) the similarity of abuse and ill effects of such substance to any other substance in Schedule I, II, III, or IV, (3) sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, and (4) an assessment of the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy.[4] None of these criteria apply to an otherwise benign product that can be converted to a dangerous substance.

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[1] 51 Fed. Reg. 35326, 35327 (October 2, 1986).
[2] Id.
[3] 21 C.F.R. § 346.12.
[4] 1971 UN Convention on Psychotropic Substances, Article 2, 4. (Full citations to the Convention are omitted for the remainder of this submission.)

Under the Vienna Convention only a significant health problem appears to be a "public health" problem.[5] As noted earlier, we are not aware of a significant problem with legitimate ephedrine-containing nonprescription medicines in the U.S. FDA, after extensive review, has already found that ephedrine is generally recognized as safe and effective for more than one nonprescription use. Furthermore, the WHO recommendation does not provide sufficient evidence of ephedrine abuse or risks to show a significant public health problem.[6]

The International Narcotics Control Board (INCB) background paper referenced in the WHO recommendation provides only inferential links between ephedrine and abuse of the ingredient itself.[7] The INCB background paper discusses unauthorized importation, seizures, and suspicious shipments, but, in the end, it is based on the assumption that the presence of quantities in excess of those anticipated for expected medical use translates to the fact that the substance itself is being abused. The INCB background paper does not provide any evidence of, nor does it focus on any public health problem from abuse of the ingredient.

The WHO recommendation states that an ephedrine problem appears to be particularly serious in certain African countries.[8] However, it is clear that of the 50 countries returning an ephedrine questionnaire to WHO, 12 indicated some problem with ephedrine, only one of which was an African country.[9] Nevertheless, it is questionable whether the fact that 12 countries have some degree of problem equates to a widespread health problem that an international agreement such as the UN Convention on Psychotropic Substances is designed to address.

WHO has not presented hard data indicating a public health problem with ephedrine abuse. Lacking such data, the WHO recommendation should be rejected.

U.S. Laws Already Meet the Obligations Under the UN Convention.

Ephedrine is a listed chemical under the Controlled Substances Act and is subject to regulations enforced by the Drug Enforcement Administration (DEA).[10] While we urge the U.S. government to oppose or defer scheduling of ephedrine by the UN Commission, we suggest

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[5] See Commentary on the Convention on Psychotropic Substances, 1971, United Nations Publication E.76.XI.5, at 46.

[6] See WHO notification on l-ephedrine, and d,l-ephedrine, Reference: NAR/CL.18/1998 CU 98/215, TLAB/CSSS/303/98, UNDCP 42nd CND, WHO/ECDD 31 (1971C), Annex II, at 2-3.

[7] See International Narcotics Control Board background paper for Dr. Cortes-Maramba, fax dated June 22, 1998. (Emphasis added.)

[8] WHO notification, supra, Annex II, at 2.

[9] Id.

[10] 64 Fed. Reg. 1629, 1633 (January 11, 1999), citing 21 U.S.C. 802(34) and 21 CFR 1309, 1310, and 1313.

that these controls are adequate to ensure that the U.S. fulfill its obligations under the UN Convention, assuming ephedrine is so scheduled.[11]

Additionally, the Chemical Diversion and Trafficking Act of 1988, the Domestic Chemical Diversion Control Act of 1993, and the Comprehensive Methamphetamine Control Act of 1996 (CMCA) were enacted to help combat the diversion of precursor chemicals, including ephedrine, for clandestine methamphetamine production. The DEA has extensive powers under these laws to address diversion of ephedrine to persons engaged in methamphetamine production.[12]

CMCA provisions include:

- Makes the possession of list I chemicals a crime in instances were the chemicals were obtained under a registration that was suspended or revoked.
- Extends federal "long arm" jurisdiction for certain controlled substance offences to include the manufacture and distribution of listed chemicals outside the U.S. with intent to illegally import them.
- Establishes higher maximum penalties for the manufacture, import, export, possession or distribution of chemicals or equipment used in methamphetamine production (10 years for a first offense and 20 years for a subsequent offense). The law also directs the sentencing commission to review and amend sentencing guidelines for methamphetamine offenses and to enhance penalties for offenses involving list I chemicals.
- Imposes a civil fine of up to $250,000 for any firm which distributes a laboratory supply to a person who uses it in a clandestine lab, where the distribution is with "reckless disregard" for the intended illicit use.
- Enhances the Attorney General's injunctive authority and establishes new injunctive authority relating to various violations of the Controlled Substances Act, including certain violations relating to listed chemicals and other chemicals, products, and equipment used in the manufacture of controlled substances.
- Includes provisions for the restitution of cleanup costs by a defendant convicted of offenses involving clandestine methamphetamine labs.

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[11] 64 Fed. Reg. 1629, 1633 (January 11, 1999).

[12] DEA has noted the CMCA replaces rules by DEA in this area with a more comprehensive system of controls relating to distribution, importation, and exportation of combination ephedrine products (single ingredient ephedrine products were already covered) and two other nonprescription drug ingredients, along with other strong tools to attack illicit diversion. See 62 Fed. Reg. 52294 , 52296 (October 7, 1997).

- Establishes advisory panels and task forces to evaluate methamphetamine education and prevention programs, to monitor methamphetamine abuse within the U.S., and to develop programs to aid industry in better identifying suspicious orders.
- Subjects ephedrine-combination products to a 24 gram, single-transaction limit for registration, recordkeeping, and reporting under the Controlled Substances Act (single ingredient ephedrine products were already covered). DEA has issued an interim rule temporarily exempting retail distributors of ephedrine-combination products from the registration requirements for single transaction sales below 24 grams of ephedrine base, and has issued a proposed rule to make the exemption permanent.
- Mail order distributors must report to DEA all sales of ephedrine (and two other nonprescription drug ingredients) to "non-regulated" persons on a monthly basis.

We believe that in comparison to the relevant UN Convention articles, the foregoing controls meet, and in some cases exceed, U.S. obligations under the UN Convention even if ephedrine were scheduled by the UN Commission. ***

A finding that the U.S. framework of laws and regulations controlling ephedrine meets the U.S. obligations under the Convention is in line with Congress' intent in the CMCA. Such intent being the continued accessibility of these products to consumers. Given the importance of such accessibility, Congress did not make ephedrine-containing products subject to a controlled substance schedule requiring a prescription.

The framework of U.S. laws and regulations illustrates a thoroughly considered approach to ephedrine control and mirrors the intent of Congress to limit large scale diversion of ephedrine for the manufacture of illicit substances, while maintaining consumer accessibility to legitimate OTC products. The WHO recommendation to the UN Commission threatens these decisions made by Congress and the FDA. We strongly urge the U.S. government to oppose the WHO recommendation.

U.S. Laws Provide Sufficient Cause for an Article 3 Exemption Under the UN Convention.

In making its ephedrine recommendation, WHO notes that ephedrine combination products would be eligible for exemption under the UN Convention.[13] As you are now aware, U.S. laws and regulations controlling ephedrine are quite extensive. Therefore, if ephedrine is scheduled under the UN Convention despite U.S. objections, and it is erroneously determined

that U.S. laws do not fulfill the obligations thereunder, U.S. laws should still be deemed to provide sufficient cause for an Article 3 Exemption. Accordingly, the U.S. should notify the UN Commission of an Article 3 exemption for legitimate ephedrine products in the U.S.

We believe other approaches are preferable to an exemption. Nevertheless, given the safe and effective approved uses of ephedrine, we submit that nonprescription ephedrine combination products, or nonprescription ephedrine in dosage forms such as creams or ointments for hemorrhoids, meet the grounds for exemption under Article 3 of the UN Convention. Such products are made in such a way as to prevent abuse. In addition, given the DEA's 24 gram retail limitation on single transactions of ephedrine-containing products without triggering registration, recordkeeping, and reporting requirements, Article 3's direction that quantities subject to abuse not be exempted would be satisfied.

If Common Sense Does Not Prevail, Adopt Qualified Scheduling of Ephedrine.

To be sure, Bayer is confident that there are strong reasons to oppose the scheduling of ephedrine under the UN Convention. However, in the alternative, if ephedrine must be scheduled, such scheduling should be on Schedule IV and only preparations that are in excess of a specified dosage or in a specified form should be included. For example, as recommended by the Nonprescription Drug Manufacturers Association (NDMA), only ephedrine at greater than 25 mg per dosage unit or in single active ingredient form for oral ingestion (i.e., not in therapeutically useful combination products for oral ingestion at 25 mg or less per dosage unit, or ephedrine sulfate in creams, lotions, or ointments to relieve swelling associated with hemorrhoids) should be scheduled.

The UN Convention supports qualified scheduling if the adverse effect and risk factors under Article 2 are found inapplicable to certain preparations. In submitting the UN Convention to the U.S. Senate, President Nixon stated that "the use of psychotropic substances for medical and scientific purposes is indispensable and . . . their availability for such purposes should not be unduly restricted."[14] A limitation by the UN Commission of a scheduled substance to a threshold dosage or particular form would be entirely consistent with U.S. policy and compatible with the authority under Article 3(3) for parties to exempt certain preparations of substances listed under the UN Convention.

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[13] See WHO notification, supra, Annex II, at 3.

[14] Letter of Submittal (June 18, 1971), "Convention on Psychotropic Substances," Executive G, 92nd Cong., 1st Sess. (June 29, 1971).

The UN Convention does not contain any provision that is inconsistent with the qualified scheduling of ephedrine. The term "substance" is not a defined term. Therefore, there are no explicit requirements that scheduling cover all forms and quantities of a particular chemical. While the UN Convention does define "psychotropic substance" (any substance, natural or synthetic, or any natural material that the Commission adds to Schedules I through IV), and "preparation," nothing in the definitions expressly precludes one or more preparations of ephedrine based on dosage or form from being excluded from listing at the same time that other preparations are treated as psychotropic substances.

Although WHO did not directly address this approach in its notification, WHO did note that ephedrine combination products would be eligible for exemption.[15] This is certainly not inconsistent with a qualified scheduling approach and would reach the same result.

Conclusion.

A decision by the UN Commission to schedule ephedrine under the UN Convention would run counter to U.S. policies. The WHO notification making this scheduling recommendation is flawed. The recommendation (1) does not provide hard data to support its conclusion, (2) confuses the roles of two different UN Conventions and (3) was developed under a process that suffers from a lack of transparency. The latter denied full and thorough input from interested parties.

The U.S. should actively oppose the scheduling of ephedrine. If, however, ephedrine is scheduled, such scheduling should be qualified to exempt legitimate, ephedrine-containing combination products and ephedrine non-ingested dosage forms. Alternatively, we suggest a finding that the existing U.S. laws and regulations controlling ephedrine meet our obligations under the UN Convention. Finally, at the very least, the U.S. should secure an exemption under Article 3 of the UN Convention.

Thank you for considering our views. We at Bayer Corporation are hopeful that this matter will be favorably resolved at the Commission's March 1999 meeting in Vienna.

Sincerely,

Gary S. Balkema /jb

Gary S. Balkema

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[15] See WHO notification, supra, Annex II, at 3.

Endnotes

* *While concerns have been expressed from time to time about ephedrine in nonprescription drug products, at an August 27-28, 1996 meeting of the FDA Food Advisory Committee, a Center for Drug Evaluation official stated that FDA has no reports of significant adverse reactions associated with ephedrine-containing OTCs used for their intended bronchodilator use. (See FDA Food Advisory Committee transcript, volume II, Wednesday, August 28, 1996, at 116-7, (quoting Dr. Michael Weintraub, Director, Office of Drug Evaluation V, FDA).*

** *The WHO report on which the recommendation is based does not provide actual evidence of abuse of the ingredient – the basis on which scheduling recommendations are to be made under the UN Convention on Psychotropic Substances. Rather, the recommendation is based on presumptions, and implies that diversion of ephedrine for use as a precursor chemical is also a factor. Suggestions that diversion of ephedrine were part of the WHO recommendation indicates that the WHO recommendation confuses the separate, distinct roles of two different conventions – the UN Convention on Psychotropic Substances and the UN Convention Against Traffic in Illicit Narcotic Drugs and Psychotropic Substances. The UN Convention is, and should remain, focused on risk benefit analysis of substances themselves and not on substances as precursors.*

This falls short of the type of significant public health problem the Psychotropic Convention is intended to address.

*** *Article 8 -- Licenses: Manufacturers, wholesalers, and distributors already need to register (the U.S. license equivalent), except for a temporary exemption (proposed as permanent) for retail distributors for single transaction sales below 24 grams of ephedrine base. Beyond that, it is unclear whether "distribution" in Article 8 is intended to apply at the retail sales level, as opposed to the wholesale distribution level. Since Article 9, discussed below, specifically refers to supply for use by individuals and retail distributors, the implication is that Article 8's open-ended "distribution" reference is focused on the wholesale distribution level. If so, U.S. mail order requirements and the existence of any retail threshold exceed our UN Psychotropic Convention obligations.*

Article 10 -- Package Warnings, Advertising: Nonprescription medicines containing ephedrine already include label information needed for safe use of the product. As to advertising, the UN Convention notes constitutional considerations must be taken into account. It does not mandate an advertising prohibition. (Indeed, it could not – a discussion well beyond the subject of FDA's notice.)

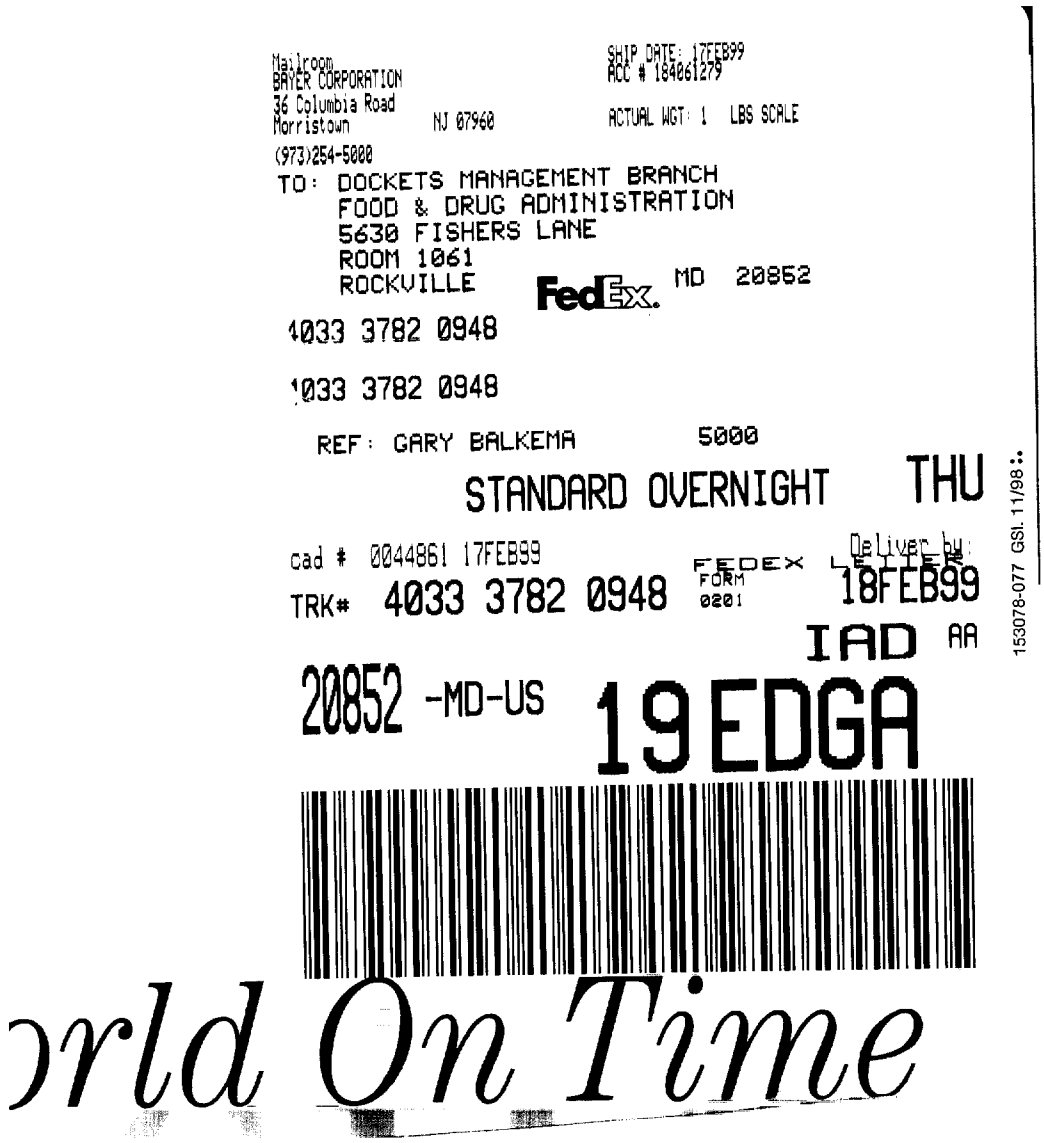
Article 11 -- Records: Manufacturers, exporters, and importers are already subject to record-keeping requirements. For that matter, so are distributors and retailers exceeding the single transaction 24 gram exemption – requirements beyond the UN Convention.

Article 9 -- Prescriptions: It is true that the current framework for ephedrine does not require that it be supplied only with a medical prescription, as the UN Convention on Psychotropics would suggest. But the UN Convention provides authority for a party to allow pharmacists or other retail distributors to supply, without prescription, Schedule IV substances in small quantities. Further, Article 5, paragraph 3 notes that it is "desirable" – not mandatory -- that parties do not permit possession of Schedule IV substances except under legal authority. DEA's 24 gram single transaction sales exemption meets the thrust of the UN Convention's intent, particularly since, going beyond the UN Convention, U.S. retailers have a duty to report "suspicious transactions" of ephedrine even apart from the 24 gram exemption rule and since wholesalers and distribution centers are subject to registration and record-keeping requirements. In addition, nine individual states require retailers to register or obtain a permit to sell nonprescription medicines (including ephedrine-containing products), and a 10th state requires retailers receiving shipments of certain nonprescription medicines from outside of the state to register.

Articles 12 and 13 – Import and Export Registration and Requirements: Current U.S. law already imposes registration requirements for importers and exporters of ephedrine. Even if adopted, the WHO recommendation to place ephedrine in Schedule IV would not require the U.S. or any other party to impose import/export control requirements. Article 12 imposes certain export control and/or import/export declaration requirements only for substances listed under Schedules I, II, and III of the Convention, not Schedule IV. Further, existing U.S. law provides ample authority for export requirements in the event that a party notifies WHO under Article 13 of the Convention that the state is prohibiting imports of a Schedule IV substance.

Article 15 – Inspection: Under existing federal and/or state law, manufacturers, exporters, importers, and wholesale and retail distributors are subject to inspection by government authorities.

Article 22 -- Penal Provisions: Ephedrine is already subject to the types of considerations expressed in this Article.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